Possibilities of treatment of patients with chronic obstructive pulmonary disease: long-term follow-up results after the use of beta-glucans

Objective — to study long-term follow-up results after the use of beta-glucans in chronic obstructive pulmonary disease (COPD) patients with frequent exacerbations.

Materials and methods. 42 patients with COPD (group C according to the GOLD classification) were under our supervision for 2 years. Patients had 2 to 4 clinical exacerbations during the previous year. They have been randomized into 2 groups with beta-glucans treatment and without it.

Results and discussion. In the patients with COPD a significant decrease in the indicators of cellular immunity was observed, which was manifested primarily by a decrease in the number of cells with natural killer activity and cells of the monocyte-macrophage series, as well as a significant decrease in the immunoregulatory ratio CD4⁺/CD8⁺. As a result, after 1 year of observation 2 patients progressed to a more severe COPD stage (from the second to the third due to repeated infectious exacerbations), and after 2 years — another 3 (15.0 %).

The prescription of beta-glucans leads to the increasing of cells with the activity of natural killers (p < 0.05) and cells of the monocyte-macrophage pull (CD14⁺, p < 0.05), and to the normalization of the CD4⁺/CD8⁺ index (p < 0.05). These changes were largely leveled off by the end of the second year of observation. The use of Immunsil D3 (Nutrimed, Ukraine) for 1 month reduced the number of exacerbations of COPD (p > 0.05) and significantly reduced the need for antibiotics prescription in patients with COPD (p < 0.05) within 1 year after treatment. During the next year of observation, the difference between the groups was significantly less pronounced.

Conclusions. Prescription of beta-glucans can be recommended for patients with COPD with frequent clinical exacerbations (groups C and D). It is needful to repeat the course of treatment with beta-glucans annually in patients with frequent clinical exacerbations of COPD.

Keywords
Chronic obstructive pulmonary disease, beta-glucans, immunity.
tially linked to COPD. Shortness of breath, which initially appears only during physical exertion, begins to bother the patient on average 5—8 years after the onset of cough. However, in some cases, the onset of the disease is possible with shortness of breath or almost simultaneous appearance of cough and shortness of breath [1].

Usually, most patients go to a doctor for the first time when a clinical picture of the disease already formed, which significantly limits the possibility of effective treatment. To a large extent, this is due to insufficient active detection of initial COPD in the early stages of the disease. According to the Ministry of Health of Ukraine, in 2019, about 380,000 patients with this disease were registered in our country. And according to epidemiological forecasts, the estimated number of patients is more than 2 million. That is, only one of every seven patients is diagnosed on time. At the same time, the expected average life expectancy of a patient with COPD after establishing the second group of disability is an average of 5—6 years [1, 11].

When choosing treatment tactics for patients with COPD, they are usually guided by the following basic principles:

– elimination of factors that cause the progression of the disease, first of all, is smoking;
– in the exacerbation phase of COPD, therapy should be aimed at eliminating the inflammatory process in the bronchi, improving bronchial patency, and restoring impaired general and local immunological reactivity;
– anti-relapse and maintenance therapy, which is also largely aimed at restoring the immunological reactivity of the patient’s body and respiratory function [11].

Categorical cessation of smoking is a primary measure that significantly improves the prognosis of the disease. This step takes a starting place in the treatment of patients with COPD. Quitting smoking reliably reduces the degree and rate of decline in external respiratory function indicators, including forced expiratory volume in the first second (FEV1) [9]. The use of inhaled bronchodilators is mostly carried out by using metered aerosols with inhalers or spacers, and dry powders [1, 5].

First-line medications in the treatment of COPD are inhaled M-cholinomimetics. They are characterized by a more pronounced bronchodilator effect and a minimal risk of adverse reactions compared with other groups of bronchodilators (especially beta 2-agonists); the low intensity of their penetration through the mucous membranes during inhalation limits the development of systemic side effects. Among the M-cholinergic blockers, tiotropium is the most widely used. The appointment of this agent contributes to a reliable improvement in the quality of life, compared to patients in the placebo group (the studies were conducted against the background of patients taking basic respiratory drugs, except for anticholinergics). Significant clinical improvement also referred to significant improvement in physical activity indicators, subjective manifestations of disease symptoms, and even improvement on the depression scale [5].

But in recent years, it turned out that the number of exacerbations is a cardinal criterion that determines not only the quality of life but also the severity of symptoms and the prognosis of the disease, as well as decisively affects the life expectancy of patients [3, 8, 16]. A severe exacerbation of the disease can lead to acute respiratory failure and cause the death of patients with COPD [12—14]. According to international statistics, the in-hospital mortality of patients with an exacerbation of COPD is 8%, and a year after the exacerbation — it is 23% [12, 15].

Clinicians know that after an exacerbation, even with adequate treatment, it is difficult and almost impossible to restore lung function to the initial level [12, 15]. Increasing shortness of breath and weakness limit the patient’s performance of usual physical activities and lead to detraining and muscle atrophy, while chronic hypoxemia and changes in the rheological properties of blood contribute to the disruption of microcirculation in the lungs, myocardium, and other organs and systems [18, 21]. The medical burden on the patient and the costs of his treatment are increasing significantly. That is why reducing the frequency of exacerbations is the goal of long-term COPD therapy, and reducing the cost of treating exacerbations in the future will limit the economic burden of COPD at the national level [3, 6, 9, 16].

It was this fact that at one time became the basis for the introduction of a fundamentally new clinical classification of COPD (ABCD), which takes into account not only the violation of the function of external breathing but also the frequency of exacerbations of the disease [1, 11]. At the same time, it should be remembered that from half to two-thirds of the total number of exacerbations are infectious, that is, they are clearly related to the development of a viral or viral-bacterial inflammatory process in the bronchi against the background of a violation of local (mucosal) immunity [3, 4]. At the same time, permanent persistent low-intensity inflammation involves not only the bronchopulmonary system — it affects almost the entire body. That is why, during some exacerbations of COPD, the so-called «low-intensity systemic sensation» is formed, which is accompanied by a significant increase in the risk of myocardial infarction, heart failure, malignant neoplasms (primarily lung cancer), pneumonia, and type
2 diabetes. That is why the development of fundamentally new approaches to reducing the frequency of exacerbations of COPD is a fundamental task. It should be remembered that the conclusions about the effect of the drug both on the mortality rate and on the frequency and risk of exacerbation can be evaluated only during long-term studies based on the data of each specific case [1, 21]. Long-term follow-up with an evaluation of treatment results is especially important.

One of the promising areas of correction is the use of immunotropic agents, which, due to their effect on mucosal immunity, can reduce the frequency of exacerbations of COPD [1]. Among immunostimulants, beta-glucans occupy a special place — pleiotropic modifiers of the immune response, more often of bacterial (rarely — plant) origin [4, 17, 20]. They consist of D-glucose monomers connected by beta-glycosidic bonds, which are not fermented in the gastrointestinal tract. The special three-dimensional structure of beta-glycans (the presence of PAMP — pathogen-associated molecular patterns) [22] ensures their targeted interaction with dectin receptors on the surface of macrophages immediately after absorption and active transfer to the submucosal layer [17]. The result is the strengthening of the phagocytic function of cells of the monocyte-macrophage series not only in the intestines but in almost all tissues [4, 7].

In addition, the activation of macrophages and natural killer cells (NK cells) by beta-glycans almost immediately triggers a whole cascade of pleiotropic effects, mostly due to the release of pro-inflammatory cytokines. Part of the beta-glycans that were absorbed in the intestine enters the liver through the portal bloodstream and through interaction with Kupffer stimulating the mechanisms of systemic immunity [4]. However, the dominant aspect of the immunostimulating effect of beta-glucans is the stimulation of local (mucosal immunity) due to the restoration of the phagocytic activity of macrophages, ensuring the completion of phagocytosis (synthesis of reactive oxygen compounds in lysosomes), increasing the production of secretory immunoglobulin A, etc. [7, 19]. Unlike traditional stimulants of phagocytosis, beta-glucans do not stimulate autoimmune and allergic reactions. Their use is highly safe, as it practically eliminates the risks of excessive stimulation of the immune response [19]. It was these aspects that prompted us to use the new beta-1,3/1,6-glucan preparation Immunsil D3 (Nutrimed, Ukraine) in patients with frequent exacerbations of COPD.

Objective — to observe long-term follow-up results after the use of beta-glucans in chronic obstructive pulmonary disease patients with frequent exacerbations.

Materials and methods

40 patients with COPD (group C according to the GOLD classification) were under our supervision for 2 years. Patients had from 2 to 4 clinical exacerbations during the previous year. They were randomized into 2 groups, matched by age, gender and clinical characteristics. Severity of the course, frequency of exacerbations, stratification of symptoms, and measurement of external breathing parameters (forced expiratory volume in the first second, forced vital capacity of the lungs and their ratio) were carried out in accordance with GOLD 2020 recommendations [1, 11]. Components of the cell immunity were studied with lymphocyte differentiation clusters determination using a Beckman Coulter flow cytometer.

Patients of the 1st group (20 patients received tiotropium bromide) and standard treatment of exacerbations, according to the COPD treatment protocol. 20 people of the 2nd group at the beginning of observation additionally received Immunsil D3 1 capsule 2 times a day for 1 month. Previously, we have presented the results of one-year follow-up of these patients for 1 year [2]. However, in the course of further monitoring of the patients, we found that in most patients (non-responders) by the end of the second year of observation, the therapeutic effect of beta-glucans was practically lost. Therefore, we summarized the results of remote observations and compared them with previously obtained data. External respiratory function and clinical severity according to the CAT scale were assessed at the beginning of treatment, after 1 year and after 2 years (at the end of the observation period). Indices of external breathing function did not significantly change in both groups, no significant difference was found between spirometric indicators in the control (1st) and experimental (2nd) groups (p > 0.05, Table 1). However, in the 1st group, after 1 year of observation, 2 patients progressed to a more severe COPD stage (from the second to the third due to repeated infectious exacerbations), and after 2 years — another 3 (15.0 %). Thus, during 2 years of observation, only 5 patients (25.0 %) progressed to severe COPD. At the same time, among the patients of the 2nd group during the first year of observation, there was not a single case of transition to a more severe degree of COPD. However, during the following year, there were 2 such patients (10 %). According to the SAT questionnaire, in the 1st (control) group, there was also a tendency to aggravation — worsening of the severity indicator in 5 patients during the first year of observation (10.0 %) and in another 4 during the next (in total — in 9 patients during 2 years). At the same time, in patients treated with the drug Immunsil D3, the SBP
index worsened in only 1 patient during the first year of observation (5.0 %) and in 3 more during the next (in total — in 4 patients during 2 years).

In the patients of the 1st group, a significant decrease in the indicators of cellular immunity was observed (Table 2), which was manifested primarily by a decrease in the number of cells with natural killer activity (p < 0.05 compared to the norm) and cells of the monocyte-macrophage series (CD14+, p < 0.05 relative to the norm), as well as a significant decrease in the immunoregulatory ratio CD4+/CD8+ (p < 0.05 relative to the norm).

During 1 year of observation, these indicators did not recover, moreover, a tendency to further decrease of the immunoregulatory ratio CD4+/CD8+ (p < 0.05 relative to the norm).

During 1 year of observation, these indicators did not recover, moreover, a tendency to further decrease of the immunoregulatory ratio CD4+/CD8+ was observed (p > 0.05 in dynamics). In contrast, the appointment of Immunsil D3 ensured an increase in the number of cells with the activity of natural killers (p < 0.05 compared to the norm) and cells of the monocyte-macrophage series (CD14+, p < 0.05 relative to the norm), as well as a significant decrease in the immunoregulatory ratio CD4+/CD8+ (p < 0.05 relative to the norm).

An adequate comparison of the immunological picture in patients after two years of follow-up was not possible due to the significant diversity of immunological changes in patients who received treatment with the drug Immunsil D3 2 years before. Some of them (responders) maintained positive changes after treatment, but in the majority (non-responders) these changes leveled off by the end of the second year of observation. These results certainly require further research. The most important result of the use of immunostimulating therapy was a significant reduction in the frequency of exacerbations from 2.6 ± 0.5 during the previous year to 1.8 ± 0.4 after a one-month course of treatment with the drug Immunsil D3 (p > 0.05, but it is likely that the difference was would be reliable in the case of an increase in the number of observations). At the same time, the frequency of exacerbations of COPD in the control group did not change at all: 2.5 ± 0.6 before observation and 2.7 ± 0.6 during the next year (p > 0.05). During the second year of observation, no significant difference was observed between the frequency of exacerbations in patients of the 1st (2.1 ± 0.5) and 2nd (2.8 ± 0.6) groups (p > 0.05), although the tendency remained to a lower frequency of exacerbations, in patients who were treated with beta-glucan 2 years ago. Instead, the need to use antibiotics in patients of the 2nd group decreased significantly. In patients treated with Immunsil D3 — from 2.3 ± 0.3 to 1.1 ± 0.2 (p < 0.05) courses of antibiotic therapy, while in the control group the need for antibiotics remained constant: 2.4 ± 0.5 before observation and 2.2 ± 0.3 during the next year (p > 0.05). That is, the number of exacerbations in patients treated with

Table 1. Dynamics of progression of COPD against the background of different treatment regimens

<table>
<thead>
<tr>
<th>Index</th>
<th>1st group (n = 20)</th>
<th>2nd group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transition to a more severe degree of COPD, patients</td>
<td>During the 1st year: 2</td>
<td>During the 1st year: 10.0</td>
</tr>
<tr>
<td>Deterioration of CAT-index, %</td>
<td>During the 2nd year: 3</td>
<td>During the 2nd year: 15.0</td>
</tr>
<tr>
<td>Deterioration of CAT-index, %</td>
<td>Totally: 5</td>
<td>Totally: 25.0</td>
</tr>
<tr>
<td>Deterioration of CAT-index, %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. * p < 0.05 vs the control group.

Table 2. Indices of immunocyte populations in patients with COPD against the background of different treatment regimens

<table>
<thead>
<tr>
<th>Index</th>
<th>1st group (n = 20)</th>
<th>2nd group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3+ cells, %</td>
<td>Before treatment: 46.89 ± 4.18</td>
<td>Before treatment: 48.67 ± 4.62</td>
</tr>
<tr>
<td>CD4+ cells, %</td>
<td>1 year after: 47.11 ± 3.84</td>
<td>1 year after: 49.15 ± 5.56</td>
</tr>
<tr>
<td>CD8+ cells, %</td>
<td>Before treatment: 36.76 ± 3.33</td>
<td>Before treatment: 36.30 ± 3.33</td>
</tr>
<tr>
<td>CD16+ cells, %</td>
<td>1 year after: 33.33 ± 2.25</td>
<td>1 year after: 32.07 ± 4.06</td>
</tr>
<tr>
<td>CD14+ cells, %</td>
<td>Before treatment: 14.14 ± 1.27</td>
<td>Before treatment: 15.68 ± 1.27</td>
</tr>
<tr>
<td>CD16+56+ cells, %</td>
<td>1 year after: 13.33 ± 0.08</td>
<td>1 year after: 12.4 ± 0.11</td>
</tr>
<tr>
<td>CD4+/CD8+</td>
<td>Before treatment: 1.11 ± 0.08</td>
<td>Before treatment: 4.44 ± 0.26</td>
</tr>
</tbody>
</table>

Note. * p < 0.05 vs before treatment; # p < 0.05 vs the control group.
the drug Immunsil D3 decreased mostly due to infectious variants. During the second year of observation, the difference regarding the need for antibiotic therapy was not so significant: 1.8 ± 0.6 in the first group and 2.3 ± 0.4 in the second (p > 0.05). Thus, prescribing Immunsil D3 1 capsule twice a day for 1 month may be useful for COPD patients with frequent clinical exacerbations (groups C and D).

At the same time, the effectiveness of the therapeutic effect of a 1-month course of beta-glucans was significantly more pronounced during the first year after the course of treatment and significantly less during the following, second year. The results obtained by us indicate the expediency of repeating the course of treatment with beta-glucans annually in patients with frequent clinical exacerbations of COPD.

Conclusions

1. The prescription of beta-glucans leads to the increasing of cells with the activity of natural killers (p < 0.05) and cells of the monocyte-macrophage pull (CD14, p < 0.05), and to the normalization of the CD4+ /CD8+ ratio (p < 0.05). These changes were largely leveled off by the end of the second year of observation.

2. The use of Immunsil D3 for 1 month reduced the number of exacerbations of COPD (p > 0.05) and significantly reduced the need for antibiotics prescription in patients with COPD (p < 0.05) within 1 year after treatment. During the next year of observation, the difference between the groups was significantly less pronounced.

3. Prescription the drug Immunsil D3 in 1 capsule twice a day for 1 month can be recommended for patients with COPD with frequent clinical exacerbations (groups C and D).

4. The results obtained by us indicate that it is needful to repeat the course of treatment with beta-glucans annually in patients with frequent clinical exacerbations of COPD.

References


Можливості лікування пацієнтів із хронічним обструктивним захворюванням легень: віддалені результати спостереження після застосування бета-глюканів

Мета роботи — вивчити віддалені результати після застосування бета-глюканів у пацієнтів із хронічним обструктивним захворюванням легень (ХОЗЛ) з частими загостреннями.

Матеріали та методи. Під нашим спостереженням протягом 2 років перебували 42 пацієнти з ХОЗЛ (група С за класифікацією GOLD). Пацієнти мали від 2 до 4 клінічних загострень протягом попереднього року. Вони були рандомізовані на дві групи: з лікуванням бета-глюканами та без нього.

Результати та обговорення. У хворих на ХОЗЛ спостерігалося достовірне зниження показників клітинного імунітету, що виявлялося насамперед зменшенням кількості клітин з природною кілерною активністю та клітин моноцитарно-макрофагального ряду, а також значним зниженням імунорегуляторного співвідношення CD4+/CD8+.

Призначення бета-глюканів сприяло збільшенню кількості клітин з активністю натуральних кілець (p < 0,05) і клітин моноцитарно-макрофагальної ланки (CD14; p < 0,05), а також нормалізації індексу CD4+/CD8+ (p < 0,05). Ці зміни значною мірою нівелювалися до кінця другого року спостереження.

Висновки. Призначення бета-глюканів можна рекомендувати хворим на ХОЗЛ з частими клінічними загостреннями (групи C і D). Необхідно щорічно повторювати курс лікування бета-глюканами у пацієнтів з частими загостреннями ХОЗЛ.

Ключові слова: хронічне обструктивне захворювання легень, бета-глюкан, імунологія.